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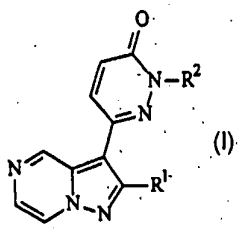
(54) Title: PYRAZOLOPYRAZINES AND THEIR USE AS ADENOSINE ANTAGONISTS



(I)

(57) Abstract: A pyrazolopyrazine compound of formula (I): wherein $R^1$ is aryl which may have one or more suitable substituent(s); and $R^2$ is hydrogen; lower alkyl; lower alkenyl; cyclo(lower)alkyl; heteromonocyclic group; lower alkyl substituted with one or more substituent(s) selected from the group consisting of cyclo(lower)alkyl, halogen, cyano, aryl and heteromonocyclic group, or a salt thereof. The pyrazolopyrazine compound (I) and salt thereof of the present invention are adenosine antagonists and are useful for the prevention and/or treatment of depression, dementia (e.g. Alhzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure and the like.

WO 01/40230 A1



DESCRIPTION

PYRAZOLOPYRAZINES AND THEIR USE AS ADENOSINE ANTAGONISTS

## TECHNICAL FIELD

The present invention relates to a novel compound and a salt thereof, which are useful as medicaments.

## BACKGROUND ART

Some pyrazolopyridine compounds to be useful as psychostimulant, remedy for renal failure, or the like are known (e.g. EP-0299209, EP-0379979, EP-0467248, EP-0516941, etc.). However, pyrazolopyrazine compounds are novel, so there has been no knowledge about these compounds.

## DISCLOSURE OF INVENTION

The present invention relates to a novel pyrazolopyrazine compound and a pharmaceutically acceptable salt thereof, which are useful as medicaments; processes for the preparation of said pyrazolopyrazine compound and a salt thereof; a pharmaceutical composition comprising, as an active ingredient, said pyrazolopyrazine compound or a pharmaceutically acceptable salt thereof; a use of said pyrazolopyrazine compound or a pharmaceutically acceptable salt thereof as a medicament; and a method for using said pyrazolopyrazine compound or a pharmaceutically acceptable salt thereof for therapeutic purposes, which comprises administering said pyrazolopyrazine compound or a pharmaceutically acceptable salt thereof to a human being or an animal.

The pyrazolopyrazine compound and a salt thereof are adenosine antagonists (especially, $A_1$ receptor and $A_2$ (particularly $A_{2a}$) receptor dual antagonists) and possess various pharmacological actions such as anticatalepsy action, cognitive enhancing action, analgesic action, locomotor action, antidepressant action, diuretic action, cardioprotective action, cardiotonic action, vasodilating action (e.g. cerebral vasodilating action, etc.), the action of increasing the renal blood flow, renal protective action, improvement action of renal

function, enhancing action of lipolysis, inhibition action of anaphylactic bronchoconstriction, acceleration action of the insulin release, the action of increasing the production of erythropoietin, inhibiting action of platelet aggregation, or the like.

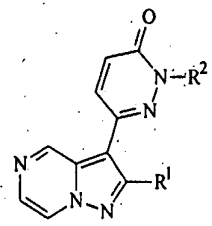
They are useful as cognitive enhancer, antianxietry drug, antidementia drug, psychostimulant, analgesic, cardioprotective agent, antidepressant, ameliorants of cerebral circulation, tranquilizer, drug for heart failure, cardiotonic agent, antihypertensive agent, drug for renal failure (renal insufficiency), drug for renal toxicity, renal protective agent, drug for improvement of renal function, diuretic, drug for edema, antiobesity, antiasthmatic, bronchodilator, drug for apnea, drug for gout, drug for hyperuricemia, drug for sudden infant death syndrome (SIDS), ameliorants of immunosuppressive action of adenosine, antidiabetic agent, drug for ulcer, drug for pancreatitis, drug for Meniere's syndrome, drug for anemia; drug for thrombosis, drug for myocardial infarction, drug for obstruction, drug for arteriosclerosis obliterans, drug for thrombophlebitis, drug for cerebral infarction, drug for transient ischemic attack, drug for angina pectoris, or the like; and useful for the prevention and/or treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure;
hypertension (e.g. essential hypertension, nephrogenous hypertension, etc.);
circulatory insufficiency (acute circulatory insufficiency) cuased by, for example, ischemia/reperfusion injury (e.g. myocardial ischemia/reperfusion injury, cerebral ischemia/reperfusion injury, peripheral ischemia/reperfusion injury, etc.), shock (e.g. endotoxin shock, hemorrhagic shock,





etc.), surgical procedure, or the like; post-resuscitation asystole;
bradyarrhythmia;
electro-mechanical dissociation;
hemodynamic collapse;
SIRS (systemic inflammatory response syndrome);
multiple organ failure;
renal failure (renal insufficiency) (e.g. acute renal failure, etc.), renal toxicity [e.g. renal toxicity induced by a drug such as cisplatins, gentamicin, FR-900506 (disclosed in EP-0184162); cyclosporin (e.g. cyclosporin A) or the like; glycerol, etc.], nephrosis, nephritis, edema (e.g. cardiac edema, nephrotic edema, hepatic edema, idiopathic edema, drug edema, acute angioneurotic edema, hereditary angioneurotic edema, carcinomatous ascites, gestational edema, etc.);
obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer such as peptic ulcer (e.g. gastric ulcer, duodenal ulcer, etc.), pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus (e.g. mechanical ileus, adynamic ileus, etc.); and
myocardial infarction, thrombosis (e.g. arterial thrombosis, cerebral thrombosis, etc.), obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, angina pectoris, or the like.

The novel pyrazolopyrazine compound of the present invention can be shown by the following formula (I).


(I)

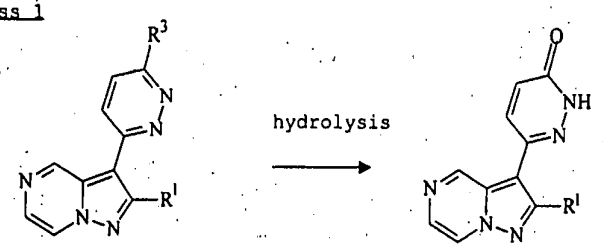
wherein $R^1$ is aryl which may have one or more suitable substituent(s), and

$R^2$ is hydrogen;
lower alkyl;
lower alkenyl;
cyclo(lower)alkyl;
heteromonocyclic group; or
lower alkyl substituted with one or more substituent(s) selected from the group consisting of cyclo(lower)alkyl, halogen, cyano, aryl and heteromonocyclic group,

or a salt thereof.

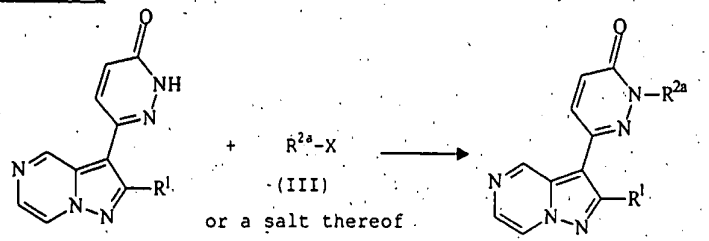
The object compound (I) or a salt thereof of the present invention can be prepared by the following processes.

Process 1




(II) or a salt thereof — (Ia) or a salt thereof

Process 2

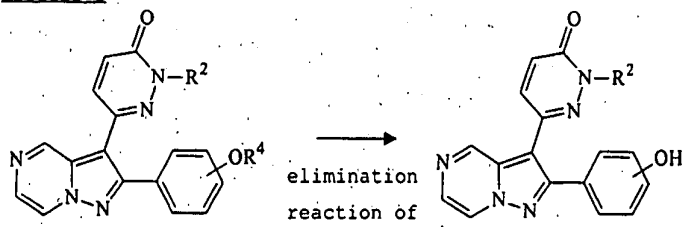



(Ia) or a salt thereof — (Ib) or a salt thereof



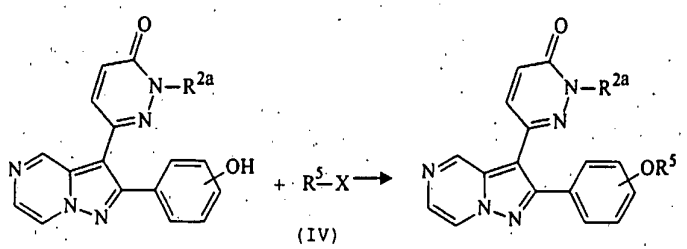


Process 3




(Ic) or a salt thereof — (Id) or a salt thereof

Process 4




(Ie) or a salt thereof — (If) or a salt thereof

wherein $R^1$ is as defined above,

$R^3$ is arylsulfonyl which may have one or more suitable substituent(s);
di(lower)alkylamino;
lower alkoxy;
lower alkylthio;
or acyloxy,

$R^{2a}$ is lower alkyl;
cyclo(lower)alkyl;
lower alkyl substituted with cyclo(lower)alkyl;
lower alkyl substituted with aryl;

heteromonocyclic group; or

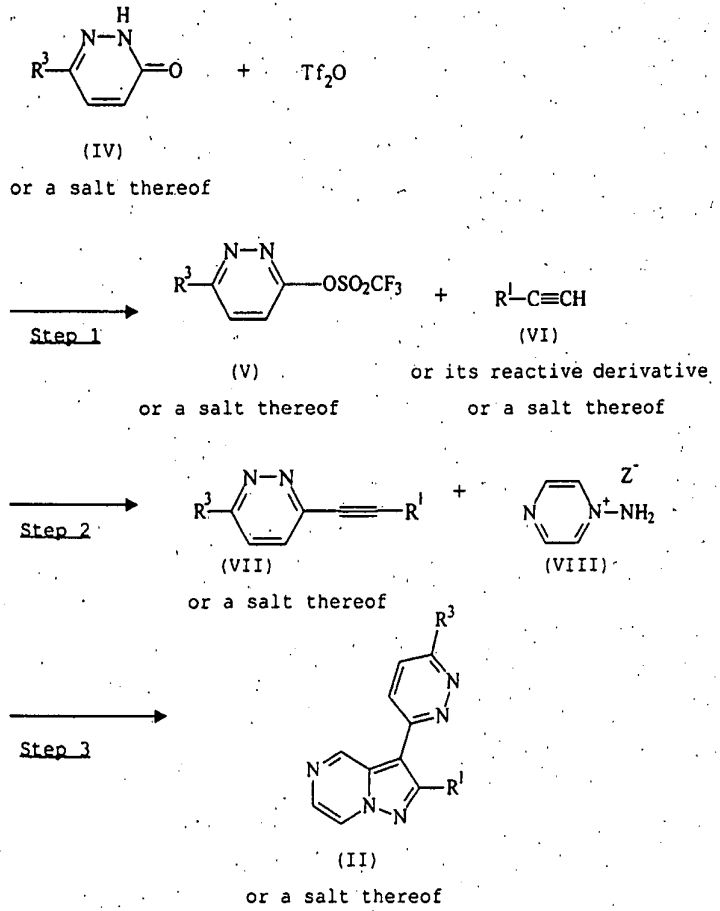
lower alkyl substituted with heteromonocyclic group,

$R^4$ and $R^5$ are each lower alkyl, and

X is a leaving group.

The starting compound(II) or a salt thereof is novel and can be prepared, for example, by the following reaction schemes.

Process A




(IV)

or a salt thereof

(V)

or a salt thereof

(VI)

or its reactive derivative

or a salt thereof

(VII)

or a salt thereof

(VIII)

(II)

or a salt thereof





wherein $R^1$ and $R^3$ is as defined above,

$Z^-$ is an anion,

$Tf_2O$ is trifluoromethanesulfonic anhydride.

In addition to the processes as mentioned above, the object compound (I) and a salt thereof can be prepared, for example, according to the procedures as illustrated in Examples in the present specification or in a manner similar thereto.

The starting compounds can be prepared, for example, according to the procedures as illustrated in Preparations in the present specification or in a manner similar thereto.

The object compound (I) and a salt thereof can be prepared according to the methods as shown in Preparations or Examples, or in a manner similar thereto.

It is to be noted that the object compound (I) may include the geometrical isomer(s) due to the double bond(s) and/or the stereo isomer(s) due to the asymmetric carbon atom(s). In this regard, one isomer can be converted to another according to a conventional method in this field of the art.

It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

Suitable salts of the object compound (I) are conventional pharmaceutically acceptable ones and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, phosphate,

etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

Suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof and which appear in the above and following description in the present specification are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched ones such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl or the like, in which the preferred one may be methyl, isopropyl or pentyl.

Suitable "lower alkenyl" may include straight or branched ones such as vinyl, allyl, isopropenyl or the like, in which the preferred one may be vinyl.

Suitable "lower alkyl substituted with halogen" may include, for example, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, fluoroethyl, chloroethyl, bromoethyl, iodoethyl, fluoropropyl, chloropropyl, bromopropyl, iodopropyl, difluoromethyl, dichloromethyl, dibromomethyl, diiodomethyl, difluoroethyl, dichloroethyl, dibromoethyl, diiodoethyl, difluoropropyl, dichloropropyl, dibromopropyl, diiodopropyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl, trifluoroethyl, trichloroethyl, tribromoethyl, triiodoethyl, trifluoropropyl, trichloropropyl, tribromopropyl, triiodopropyl, in which the preferred one may be fluoroethyl, fluoropropyl, trifluoroethyl or trifluoropropyl.

Suitable "aryl" may include phenyl, naphthyl, indenyl, anthryl, and the like, in which the preferred one may be (C6-C10) aryl, and the more preferred one may be phenyl.

The "aryl" mentioned above may have one or more (preferably 1 to 3) suitable substituent(s) selected from the group consisting of halogen (e.g. fluoro, chloro, bromo, iodo), lower alkyl as





mentioned above, lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, etc.), hydroxy, and the like.

Suitable "cyclo(lower)alkyl" may be cyclo(C3-C8)alkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or the like, in which the preferred one may be cyclo(C5-C6)alkyl such as cyclopentyl or cyclohexyl.

Suitable "heteromonocyclic group" may include saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 hetero atom(s) selected from among oxygen, sulfur and nitrogen in its ring, in which the preferred one may be saturated 5 to 6-memberd heteromonocyclic group containing 1 to 2 oxygen atom(s) in its ring such as tetrahydrofuranyl or tetrahydropyranyl; or unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 hetero atom(s) selected from among oxygen, sulfur and nitrogen in its ring, in which the preferred one may be unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 hetero atom(s) selected from among oxygen, sulfur and nitrogen in its ring such as pyridyl, furanyl, thienyl and thiazolyl.

Suitable "a leaving group" may include halogen (e.g. fluoro, chloro, bromo and iodo), hydroxy, acyloxy such as alkanoyloxy (e.g. acetoxy, propionyloxy, etc.), sulfonyloxy (e.g. mesyloxy, tosyloxy, etc.), and the like.

Suitable "anion" may be formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, chloride, bromide, iodide, sulfate, phosphate, or the like.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The compound (Ia) or a salt thereof can be prepared by subjecting the compound (II) or a salt thereof to hydrolysis.

Suitable salt of the compound (II) can be referred to an acid

addition salt as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base includes an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), the hydroxide or carbonate or hydrogencarbonate thereof, trialkylamide (e.g. trimethylamine, triethylamine, etc.), hydrazine, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid includes an organic acid (e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.).

The elimination using Lewis acid such as trihaloacetic acid (e.g. trichloroacetic acid, trifluoroacetic acid, etc.) or the like is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.).

The reaction is usually carried out in a solvent such as water, an alcohol (e.g. methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 2

The compound (Ib) or a salt thereof can be prepared by reacting





the compound (Ia) or a salt thereof with the compound (III) or a salt thereof.

Suitable salt of the compound (Ia) can be referred to an acid addition salt as exemplified for the compound (I).

Suitable salt of the compound (III) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, sec-butanol, amyl alcohol, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound (III) is in liquid, it can also be used as a solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride, organic base such as trialkylamine, and the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate, potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) or the like.

When X is -OH, activation of OH with triphenylphosphine and the like may be necessary.

Process 3

The compound (Id) or a salt thereof can be prepared by

subjecting the compound (Ic) or a salt thereof to elimination reaction of alkyl group.

Suitable salts of the compound (Ic) and (Id) can be referred to the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method such as hydrolysis.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base includes an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), hydroxide or carbonate or bicarbonate thereof, trialkylamine (e.g. trimethylamine, triethylamine, etc.), hydrazine, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid includes an organic acid (e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.).

The elimination using Lewis acid (e.g. aluminium chloride, titanium trichloride, tin tetrachloride, etc.) or the like is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.).

The reaction is usually carried out in a solvent such as water, alcohol (e.g. methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvents which do not adversely affect the reaction, or a mixture thereof. A liquid base or acid can be also used as the solvent.

The reaction of this process can be also carried out according





to a conventional reduction method employed in this field of the art (e.g. chemical reduction, catalytic reduction, etc.).

The reaction temperature is not critical and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 4

The compound (If) or a salt thereof can be prepared by reacting the compound (Ie) or a salt thereof with the compound (IV) or a salt thereof.

Suitable salt of the compound (Ie), (IV) and (If) can be referred to the ones as exemplified for the compound (I).

The reaction of this process can be carried out in the manner similar to that of Process 2.

Process A

Step 1 and 2

The reaction of this steps can be carried out by the methods disclosed in Preparation 1 and Preparation 2 mentioned later or the similar manners thereto.

Step 3

The compound (II) or a salt thereof can be prepared by reacting the compound (VII) or a salt thereof with the compound (VIII).

Suitable salts of the compounds (II) and (VII) can be referred to acid addition salts as exemplified for the compound (I).

The reaction is usually carried out in a solvent such as water, methylene chloride, ethylene chloride, N,N-dimethylformamide or any other solvent which does not adversely influence the reaction or a mixture thereof.

The reaction can be carried out in the presence of a base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), ar(lower)alkyltri(lower)alkylammonium halide (e.g. benzyltrimethylammonium chloride, etc.) or the like.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at room temperature or under

warming.

The object compound (I) of the present invention is an adenosine antagonist and possesses the various pharmacological actions as stated before.

In order to show the usefulness of the compound (I) of the present invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

Test 1 : Adenosine antagonistic activity

[I] Test method

The adenosine antagonistic activity [Ki(nM)] of the test compound was examined by radioligand binding techniques using 8-cyclopentyl-1,3-dipropylxanthine, [dipropyl-2,3-$^3$H(N)] ([$^3$H]DPCPX, 4.5nM) for human $A_1$ receptor and [$^3$H]CGS 21680 (20nM) for human $A_{2a}$ receptor.

[II] Test compound

3-[2-(Pyridin-3-ylmethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine (Example 3)

3-(2-Ethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (Example 5)

3-(2-Cyclopentyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (Example 8)

3-(2-Furfuryl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (Example 12)

3-[2-(2-Thenyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine (Example 14)

3-[2-(4-Tetrahydropyranyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine (Example 15)





[III] Test result

Table 1

| Test compound (Example No.) | Adenosine receptor binding (Ki:nM) | |
|---|---|---|
| | $A_1$ | $A_{2a}$ |
| 3 | 0.10 | 2.79 |
| 5 | 0.16 | 1.91 |
| 8 | 0.10 | 0.84 |
| 12 | 0.07 | 1.42 |
| 14 | 0.06 | 2.35 |
| 15 | 0.10 | 3.17 |

Test 2 : Anticatalepsy activity in Mouse

[I] Test method

The test compound (3.2mg/kg) was administered orally with ddY mice(n=7). Then, haloperidol (0.32mg/kg) was injected intraperitoneally 30 min. after the administration of the compound. Thirty min. after the injection, the cataleptic responses of mice were measured. The forelimbs of each mouse were placed on a 3 cm high, 3 mm wide horizontal bar, and the duration of cataleptic posture was measured for up to 30 sec.

[II] Test compound

3-(2-Ethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (Example 5)

3-(2-Cyclopentyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (Example 8)

3-(2-Furfuryl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (Example 12)

3-[2-(2-Thenyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine (Example 14)

[III] Test result

Table 2

| Test compound (Example No.) | Manifestation rate of catalepsy (number of mouse) |
|---|---|
| 5 | 1/7 |
| 8 | 0/7 |
| 12 | 0/7 |
| 14 | 2/7 |

The pyrazolopyrazine compound (I) and a salt thereof of this invention are useful as adenosine antagonists (especially, $A_1$ receptor and $A_2$ (particularly $A_{2a}$) receptor dual antagonists) and for the prevention and/or the treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, angina pectoris, and the like.

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in a





solid, semisolid or liquid form, which contains the pyrazolopyrazine compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. In addition, auxiliary, stabilizing agents, thickening agents, coloring agents and perfumes may be used where necessary. The pyrazolopyrazine compound (I) or a pharmaceutically acceptable salt thereof is included in a pharmaceutical composition in an amount sufficient to produce the desired aforesaid pharmaceutical effect upon the process or condition of diseases.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous, intramuscular, pulmonary or oral administration, or insufflation. While the dosage of therapeutically effective amount of the pyrazolopyrazine compound (I) varies depending on the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the pyrazolopyrazine compound (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.1 - 100 mg of the pyrazolopyrazine compound (I) per kg weight of a human being or an animal, and in case of oral administration, a daily dose of 0.5 - 100 mg of the pyrazolopyrazine compound (I) per kg weight of a human being or an animal is generally given for the prevention and/or treatment of the aforesaid diseases.

The following Preparations and Examples are given for the

purpose of illustrating the present invention in more detail.

Preparation 1

A mixture of 6-benzenesulfonyl-2H-pyridazin-3-one (150 g), triethylamine (115 ml) in dichloromethane (1.2 l) was stirred at -8°C. Trifluoromethanesulfonic anhydride (117 ml) was added dropwise to the above solution over 1 hour, and the whole was stirred under same conditions for 1 hour. The reaction mixture was stirred at room temperature for 2 hours. 1N-Hydrochloric acid was added to the reaction mixture, which was extracted with ethyl acetate. The extract was washed with 1N-hydrochloric acid twice, saturated aqueous sodium hydrogen-carbonate and brine, and dried over magnesium sulfate. The solvent was removed in vacuo to afford a powder, which was triturated with diisopropyl ether. Trifluoromethanesulfonic acid 6-benzene-sulfonylpyridazin-3-yl ester (200 g) was obtained by filtration.

NMR (CDCl3, δ): 7.5-7.8(4H,m), 8.1-8.2(2H,m), 8.52 (1H,d,J=9.0Hz)

APCI/MS: 369[M+H]$^+$ .

Preparation 2

A mixture of trifluoromethanesulfonic acid 6-benzene-sulfonylpyridin-3-yl ester (400 g), dichlorobis (triphenylphosphine)palladium (7.8 g), cuprous iodide (2.12 g), phenylacetylene (158 ml) and triethylamine (310 ml) in N,N-dimethylformamide (3.0 l) was stirred at room temperature. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into water (20 l) to afford a brown powder, which was triturated with diisopropyl ether (1000 ml) and ethanol (400 ml). A crude was obtained by filtration. The crude was subjected to column chromatography on silica gel eluting with chloroform to afford 3-benzenesulfonyl-6-phenylethynyl-pyridazine(160 g) as a pale yellow powder.

NMR (CDCl3, δ): 7.3-7.45(3H,m), 7.5-7.75(5H,m), 7.75-7.85(2H,m), 8.25(1H,d,J=8.8Hz), 7.81(1H,d,J=8.7Hz)





APCI/MS: 321[M+H]$^+$ .

Preparation 3

To a stirred mixture of 1-aminopyrazinium iodide (25.6 g) and 3-benzenesulfonyl-6-phenylethynylpyridazine (9 g) in N,N-dimethylformamide (150 ml) was added powder potassium carbonate (23 g) at ambient temperature. After stirring for 3 hours, the mixture was poured into water. The resultant precipitate was collected by filteration to give 3-(6-benzenesulfonyl-pyridazin-3-yl)-2-phenylpyrazolo[1,5-a]pyrazine (11.4 g)

mp: 208-210°C ($CHCl_3$-IPE)

NMR (DMSO-d6, δ): 7.51-7.83(9H,m), 8.03-8.19(3H,m), 8.33-8.38(1H,m), 8.99(1H,dd,J=1.3, 4.6Hz), 8.99(1H,d,J=1.3Hz)

IR (nujol): 1562, 1506 cm$^{-1}$

APCI/MS: 414[M+H]$^+$

Anal. Calcd for $C_{22}H_{15}N_5O_2S \cdot 0.26H_2O$:

C,63.20; H,3.74; N,16.75

Found: C,63.19; H,3.55; N,16.69.

Preparation 4

3-Benzenesulfonyl-6-(2-methoxyphenylethynyl)pyridazine was obtained in a similar manner to that of Preparation 2.

NMR (CDCl3, δ): 3.90(3H, s), 6.85-7.0(2H, m), 7.3-7.75(5H, m), 7.82(1H, d, J=8.7Hz), 8.05-8.2(2H, m), 8.22(1H, d, J=8.7Hz)

APCI/MS: 351 [M+H]$^+$ .

Preparation 5

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(2-methoxyphenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Preparation 3.

mp: >250°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 3.33(3H, s), 7.05-7.2(2H, m), 7.45-7.85(6H, m), 8.0-8.1(2H, m), 8.16(1H, d, J=4.7Hz), 8.41(1H, d, J=8.9Hz), 8.97(1H, dd, J=1.3Hz and 4.7Hz), 9.69(1H, d, J=1.3Hz)

IR (KBr, cm$^{-1}$): 1652, 1608

APCI/MS: 444 [M+H]$^+$ .

Preparation 6

3-Benzenesulfonyl-6-(3-methoxyphenylethynyl)pyridazine was obtained in a similar manner to that of Preparation 2.

NMR (CDCl3, δ): 3.83(3H, s), 6.9-7.85(9H, m), 8.1-8.35(2H, m)

APCI/MS: 351 [M+H]$^+$ .

Preparation 7

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(3-methoxyphenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Preparation 3.

mp: 231-233°C

NMR (DMSO-d6, δ): 3.72(3H, s), 7.0-8.15(10H, m), 8.18(1H, d, J=4.7Hz), 8.37(1H, d, J=9.0Hz), 8.99(1H, dd, J=1.3Hz and 4.7Hz), 9.61(1H, d, J=1.2Hz)

IR (KBr, cm$^{-1}$): 1650, 1592

APCI/MS: 444 [M+H]$^+$ .

Preparation 8

3-Benzenesulfonyl-6-(3-methoxyphenylethynyl)pyridazine was obtained in a similar manner to that of Preparation 2.

NMR (CDCl3, δ): 3.83(3H, s), 6.9-7.85(9H, m), 8.1-8.35(2H, m)

APCI/MS: 351 [M+H]$^+$ .

Preparation 9

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(4-methoxyphenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Preparation 3.

mp: 230-232°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 3.72(3H, s), 7.0-8.4(12H, m), 8.95-9.05(1H, m), 9.60-9.65(1H, m)

IR (KBr, cm$^{-1}$): 1650, 1592

APCI/MS: 444 [M+H]$^+$ .

Preparation 10

3-Benzenesulfonyl-6-(4-tolylethynyl)pyridazine was





obtained in a similar manner to that of Preparation 2.

mp: 208-211°C ($CHCl_3$)

NMR (CDCl3, δ): 2.37(3H, s), 7.32(2H, d, J=8.0Hz), 7.60(2H, d, J=8.0Hz), 7.65-7.85(3H, m), 8.08(1H, dd, J=1.6Hz and 7.0Hz), 8.25(1H, d, J=8.8Hz), 8.49(1H, d, J=8.8Hz)

IR (KBr, cm$^{-1}$): 2217

APCI/MS: 335 [M+H]$^+$ .

Preparation 11

3-Benzenesulfonyl-6-(2-chlorophenylethynyl)pyridazine was obtained in a similar manner to that of Preparation 2.

NMR (CDCl3, δ): 7.5-7.65(2H, m), 7.65-7.9(5H, m), 8.0-8.15(2H, m), 8.29(1H, d, J=8.8Hz), 8.52(1H, d, J=8.8Hz)

IR (KBr, cm$^{-1}$): 2217

APCI/MS: 355 [M+H]$^+$ .

Preparation 12

3-Benzenesulfonyl-6-(3-chlorophenylethynyl)pyridazine was obtained in a similar manner to that of Preparation 2.

mp: 149-151°C ($CHCl_3$)

NMR (CDCl3, δ): 7.25-7.75(7H, m), 7.82(1H, d, J=8.7Hz), 8.1-8.2(2H, m), 8.27(1H, d, J=8.7Hz)

IR (KBr, cm$^{-1}$): 2225, 1589

APCI/MS: 355 [M+H]$^+$ .

Preparation 13

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(3-chlorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Preparation 3.

mp: 239-241°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 7.0-9.8(14H, m)

IR (KBr, cm$^{-1}$): 1594, 1565

APCI/MS: 448 [M+H]$^+$ .

Preparation 14

3-Benzenesulfonyl-6-(2-chlorophenylethynyl)pyridazine

was obtained in a similar manner to that of Preparation 2.

mp: 177-179°C ($CHCl_3$)

NMR (CDCl3, δ): 7.2-7.75(7H, m), 7.86(1H, d, J=8.8Hz), 8.1-8.2(2H, m), 8.27(1H, d, J=8.8Hz)

IR (KBr, $cm^{-1}$): 2223

APCI/MS: 355 $[M+H]^+$ .

Preparation 15

3-Benzenesulfonyl-6-(2-fluorophenylethynyl)pyridazine was obtained in a similar manner to that of Preparation 2.

mp: 192-194°C ($CHCl_3$)

NMR (CDCl3, δ): 7.3-7.5(2H, m), 7.55-7.9(5H, m), 8.05-8.15(2H, m), 8.30(1H, d, J=8.8Hz), 8.53(1H, d, J=8.8Hz)

IR (KBr, $cm^{-1}$): 2225

APCI/MS: 339 $[M+H]^+$ .

Preparation 16

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(2-fluorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Preparation 3.

mp: 228-230°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 7.25-7.5(2H, m), 7.55-7.9(6H, m), 8.05-8.15(2H, m), 8.21(1H, d, J=4.7Hz), 8.40(1H, d, J=9.0Hz), 9.02(1H, dd, J=1.4Hz and 4.7Hz), 9.68(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1616, 1565

APCI/MS: 432 $[M+H]^+$ .

Preparation 17

3-Benzenesulfonyl-6-(3-fluorophenylethynyl)pyridazine was obtained in a similar manner to that of Preparation 2.

mp: 150-152°C ($CHCl_3$)

NMR (CDCl3, δ): 7.0-7.75(7H, m), 7.83(1H, d, J=8.7Hz), 8.0-8.2(2H, m), 8.27(1H, d, J=8.7Hz)

IR (KBr, $cm^{-1}$): 2219





APCI/MS: 339 $[M+H]^+$ .

Preparation 18

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(3-fluorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Preparation 3.

mp: 226-228°C ($CHCl_3$)

NMR (DMSO-d6, δ): 7.2-8.8(12H, m), 8.99(1H, dd, J=1.1Hz and 4.7Hz), 9.61(1H, d, J=1.1Hz)

IR (KBr, $cm^{-1}$): 1565

ESI/MS: 434 $[M+Na]^+$ .

Preparation 19

3-Benzenesulfonyl-6-(4-fluorophenylethynyl)pyridazine was obtained in a similar manner to that of Preparation 2.

mp: 189-191°C ($CHCl_3$)

NMR (CDCl3, δ): 7.0-7.2(2H, m), 7.5-7.75(5H, m), 7.80(1H, d, J=8.7Hz), 8.1-8.2(2H, m), 8.25(1H, d, J=8.7Hz)

IR (KBr, $cm^{-1}$): 2221

APCI/MS: 339 $[M+H]^+$ .

Preparation 20

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(4-fluorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Preparation 3.

mp: 218-220°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 7.3-7.45(1H, m), 7.6-7.9(7H, m), 8.0-8.2(3H, m), 8.3-8.4(1H, m), 8.98(1H, dd, J=1.4Hz and 4.7Hz), 9.60-(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1677, 1606

APCI/MS: 432 $[M+H]^+$ .

Preparation 21

3-Benzenesulfonyl-6-(4-pentyl-phenylethynyl)pyridazine was obtained in a similar manner to that of Preparation 2.

mp: 164-166°C ($CHCl_3$)

NMR (CDCl3, δ): 0.8-1.0(3H, m), 1.25-1.45(4H, m), 1.5-1.75(2H, m), 2.55-2.75(2H, m), 7.1-7.3(2H, m), 7.45-7.75(5H, m), 7.78(1H, d, J=8.7Hz), 8.1-8.2(2H, m), 8.23(1H, d, J=8.7Hz)

IR (KBr, $cm^{-1}$): 2217

APCI/MS: 391 $[M+H]^+$ .

Preparation 22

3-Benzenesulfonyl-6-(3,4-difluorophenylethynyl) pyridazine was obtained in a similar manner to that of Preparation 2.

mp: 170-172°C ($CHCl_3$)

NMR (CDCl3, δ): 7.5-8.0(6H, m), 8.0-8.2(2H, m), 8.29(1H, d, J=8.8Hz), 8.55(1H, d, J=8.8Hz)

IR (KBr, $cm^{-1}$): 2221

APCI/MS: 357 $[M+H]^+$ .

Preparation 23

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(3,4-difluorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Preparation 3.

mp: 230-232°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 7.4-8.4(11H, m), 8.99(1H, dd, J=1.4Hz and 4.7Hz), 9.61(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1606, 1565

APCI/MS: 450 $[M+H]^+$ .

Preparation 24

3-Benzenesulfonyl-6-(2,4-difluorophenylethynyl) pyridazine was obtained in a similar manner to that of Preparation 2.

mp: 192-195°C ($CHCl_3$)

NMR (CDCl3, δ): 7.2-7.35(1H, m), 7.45-7.6(1H, m),7.65-7.95(4H, m), 8.0-8.2(2H, m), 8.29(1H, d, J=8.8Hz), 8.53(1H, d, J=8.8Hz)

IR (KBr, $cm^{-1}$): 2223

APCI/MS: 357 $[M+H]^+$ .





Preparation 25

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(2,4-difluorophenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Preparation 3.

mp: 202-204°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ); 7.2-7.55(2H, m), 7.65-7.9(4H, m), 8.0-8.15(2H, m), 8.21(1H, d, J=4.7Hz). 8.3-8.5(1H, m), 9.02(1H, dd, J=1.4Hz and 4.7Hz), 9.67(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1617, 1596

APCI/MS: 450 $[M+H]^+$ .

Preparation 26

To a mixture of 3-(2-cyanomethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (4g) and triethylamine (20ml) in pyridine(40ml) was introduced hydrogen sulfide at 60°C for 35 minutes. The mixture was poured into water. The resulting solid was collected by filtration and washed with acetone to give 3-(2-thiocarbamoylmethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (3.3g).

mp: 236-237°C (acetone)

NMR (DMSO,δ): 5.08(2H,S), 6.95(1H,d,J=9.7Hz), 7.13(1H,d,J=9.7Hz), 7.50-7.54(3H,m), 7.67-7.73(2H,m), 8.08(1H,d,J=4.7Hz), 8.90(1H,d,J=1.3,4.7Hz), 9.45(1H,d,J=1.3Hz), 9.47(1H,S), 9.92(1H,S)

IR(nujol): 3241, 3100, 1670, 1592, 1531, 1500 $cm^{-1}$

ESI/MS: 385$[M+Na]^+$

Anal. Calcd for $C_{18}H_{12}N_6O$ :

C,59.66; H,3.89; N,23.19.

Found: C,59.74; H,3.84; N,22.85.

Preparation 27

3-[2-(1-tert-Butoxycarbonylpiperidin-4-yl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine was

obtained in a similar manner to that of Example 3.

mp: 165-166°C (AcOEt-hexane)

NMR(DMSO, δ): 1.40(9H,S),1.62-1.87(4H,m); 2.80-3.10(2H,m), 3.90-4.15(2H,m), 3.90-4.15(2H,m), 4.97-5.10(1H,m), 6.96(1H,d,J=9.6Hz), 7.28(1H,d,J=9.6Hz), 7.48-7.64(5H,m), 8.09(1H,d,J=4.7Hz), 8.92(1H,dd,J=1.3,4.7Hz), 9.30(1H,d,J=1.3Hz)

IR(nujol): 1704, 1687, 1662, 1589, 1517 $cm^{-1}$

APCI/MS: 473[M+H]$^+$

Anal. Calcd for $C_{26}H_{28}N_6O_3 \cdot 0.3H_2O$:

C,65.34; H,6.03; N,17.58.

Found: C,65.35; H,5.93; N,17.63.

Preparation 28

3-Benzenesulfonyl-6-(5-fluolo-2-methoxyphenylethynyl) pyridazine can be obtained in a similar manner to that of Preparation 2.

Preparation 29

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(5-fluoro-2-methoxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Preparation 3.

Preparation 30

3-Benzenesulfonyl-6-(3-fluolo-5-methoxyphenylethynyl) pyridazine can be obtained in a similar manner to that of Preparation 2.

Preparation 31

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(3-fluoro-5-methoxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Preparation 3.

Preparation 32

3-Benzenesulfonyl-6-(3-fluolo-4-methoxyphenylethynyl) pyridazine can be obtained in a similar manner to that of Preparation 2.





Preparation 33

3-(6-Benzenesulfonylpyridazin-3-yl)-2-(3-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Preparation 3.

Example 1

A mixture of 3-(6-benzenesulfonylpyridazin-3-yl)-2-phenylpyrazolo[1,5-a]pyrazine (0.61 g), sodium hydroxide (0.25 g), water (2.5 ml) and dioxane (6 ml) was refluxed for 0.5 hours. After evaporating the solvent, the residue was dissolved in water and then the solution was acidified with 1N-hydrochloric acid. The mixture was partitioned between an aqueous sodium bicarbonate and chloroform. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was recrystallized from a mixture of chloroform and diisopropyl ether to give 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (0.41 g) as a solid.

mp: >250°C

NMR (DMSO-d6,δ): 6.88(1H,d,J=9.9Hz), 7.20(1H,d,J=9.9Hz), 7.48-7.64(5H,m), 8.07(1H,d,J=4.8Hz), 8.91(1H,d,J=4.8Hz), 9.29(1H,s), 13.28(1H,s)

IR (nujol): 1673, 1658, 1592, 1550, 1527 $cm^{-1}$

APCI/MS: 290[M+H]$^+$

Anal. Calcd for $C_{16}H_{11}N_5O \cdot 0.36H_2O$:

C,64.97; H,3.99; N,23.88

Found: C,64.86; H,3.69; N,23.63.

Example 2

To a stirred solution of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (0.19 g) in N,N-dimethylformamide (12 ml) was added 60%-sodium hydride (40 mg) at ambient temperature. After stirring for 15 minutes, isopropyl iodide (0.097 ml) was added to the mixture which was stirred for 16 hours. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried

over magnesium sulfate and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (0.135 g) as a solid.

mp: 173-175°C

NMR (DMSO-d6,δ): 1.31(6H,d,J=6.6Hz), 5.14-5.28(1H,m), 6.29(1H,d,J=9.6Hz), 7.25(1H,d,J=9.6Hz), 7.48-7.63(5H,m), 8.09(1H,d,J=4.7Hz), 8.92(1H,dd,J=1.2, 4.7Hz), 9.33(1H,d,J=1.2Hz)

IR (nujol): 1662, 1589, 1523 $cm^{-1}$

APCI/MS: 332[M+H]$^+$

Anal. Calcd for $C_{19}H_{17}N_5O$: C,68.87; H,5.17; N,21.13

Found: C,68.69; H,5.11; N,21.08.

Example 3

To a stirred mixture of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (0.19 g), 3-pyridinemethanol(0.11 ml) and triphenylphosphine(0.38 g) in tetrahydrofuran(10 ml) was added diethyl azodicarboxylate(0.23 ml) under ice-cooling. After stirring for 16 hours at ambient temperature, the solution was evaporated in vacuo. The residue was chromatographed on silica-gel(150 ml) using a mixture of methanol and ethyl acetate(1:100). The desired fractions were collected and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 3-[2-(pyridin-3-ylmethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine (0.145 g) as a solid.

mp: 158-159°C

NMR (DMSO-d6,δ): 5.43(2H,s), 6.99(1H,d,J=9.7Hz), 7.20(1H,d,J=9.7Hz), 7.38-7.80(7H,m), 8.08(1H,d,J=4.7Hz), 8.53-8.65 (2H,m), 8.90(1H,dd,J=1.2, 4.7Hz), 9.21(1H,d,J=1.2Hz)

IR (nujol): 1664, 1590, 1531 $cm^{-1}$

APCI/MS: 381[M+H]$^+$

Anal.Calcd for $C_{22}H_{16}N_6O \cdot 0.2H_2O$: C,68.81; H,4.30; N,21.88





Found: C,69.03; H,4.28; N,21.59

Example 4

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 196-197°C (AcOEt-Hexane)

NMR (DMSO-d6,δ): 3.78(3H,s), 6.92(1H,d,J=9.7Hz), 7.14(1H,d,J=9.7Hz), 7.49-7.66(5H,m), 8.09(1H,d,J=4.7Hz), 8.91(1H,d,J=4.7Hz), 9.43(1H,s)

IR (nujol): 1666, 1592, 1527, 1502 $cm^{-1}$

APCI/MS: 304[M+H]$^+$

Anal. Calcd for $C_{17}H_{13}N_5O \cdot 0.12H_2O$:

C,66.84; H,4.37; N,22.93

Found: C,66.84; H,4.26; N,22.90.

Example 5

3-(2-Ethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 160-163°C (AcOEt-Et2O)

NMR (DMSO-d6,δ): 1.33(3H,t,J=7.1Hz), 4.20(2H,q,J=7.1Hz), 6.93(1H,d,J=9.6Hz), 7.20(1H,d,J=9.6Hz), 7.49-7.65(5H,m), 8.09(1H,d,J=4.5Hz), 8.90-8.93(1H,m), 9.39(1H,s)

IR (nujol): 1664, 1589, 1519, 1506 $cm^{-1}$

APCI/MS: 318[M+H]$^+$

Anal. Calcd for $C_{18}H_{15}N_5O \cdot 0.58H_2O$:

C,65.98; H,4.97; N,21.36

Found: C,66.25; H,4.71; N,20.90.

Example 6

3-(2-Propyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 110-115°C (Et2O-Hexane)

NMR (DMSO-d6,δ): 0.93(3H,t,J=7.4Hz), 1.73-1.85(2H,m), 4.13(2H,t,J=7.1Hz), 6.93(1H,d,J=9.6Hz), 7.19(1H,d,J=9.6Hz), 7.49-7.64(5H,m), 8.09(1H,d,J=4.7Hz), 8.92(1H,d,J=4.7Hz), 9.36(1H,s)

IR (nujol): 1666, 1664, 1589, 1519, 1506 $cm^{-1}$

APCI/MS: 332[M+H]$^+$ .

Example 7

3-(2-Butyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 145-147°C (AcOEt-Et2O)

NMR (DMSO-d6,δ): 0.92(3H,t,J=7.2Hz), 1.29-1.41(2H,m), 1.70-1.79(2H,m), 4.16(2H,t,J=7.2Hz), 6.93(1H,d,J=9.6Hz), 7.20(1H,d,J=9.6Hz), 7.49-7.64(5H,m), 8.09(1H,d,J=4.4Hz), 8.90-8.93(1H,m), 9.36(1H,s)

IR (nujol): 1662, 1592, 1533, 1500 $cm^{-1}$

APCI/MS: 346[M+H]$^+$

Anal. Calcd for $C_{20}H_{19}N_5O \cdot 0.35H_2O$:

C,68.30; H,5.65; N,19.91

Found: C,68.30; H,5.57; N,19.64.

Example 8

3-(2-Cyclopentyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 163-166°C (AcOEt-Et2O)

NMR (DMSO-d6,δ): 1.15-2.15(8H,m), 5.30-5.50(1H,m), 6.91(1H,d,J=9.6Hz), 7.27(1H,d,J=9.6Hz), 7.48-7.62(5H,m), 8.08(1H,d,J=4.6Hz), 8.92(1H,d,J=4.6Hz), 9.30(1H,s)

IR (nujol): 1660, 1590, 1525, 1500 $cm^{-1}$

APCI/MS: 358[M+H]$^+$

Anal. Calcd for $C_{21}H_{19}N_5O \cdot 0.3H_2O$:

C,69.52; H,5.44; N,19.30





Found: C,69.49; H,5.26; N,19.26.

Example 9

3-(2-Cyclohexylmethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 140-145°C (AcOEt-Et2O)

NMR (DMSO-d6,δ): 0.90-2.10(11H,m), 4.00(2H,d,J=7.3Hz), 6.93(1H,d,J=9.6Hz), 7.21(1H,d,J=9.6Hz), 7.49-7.64(5H,m), 8.09(1H,d,J=4.7Hz), 8.92(1H,d,J=4.7Hz), 9.34(1H,s)

IR (nujol): 1664, 1590, 1529, 1504 $cm^{-1}$

APCI/MS: 386[M+H]$^+$

Anal. Calcd for $C_{23}H_{23}N_5O \cdot 0.34H_2O$:

C,70.55; H,6.09; N,17.88

Found: C,70.54; H,5.92 N,17.68.

Example 10

3-(2-Benzyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 144-151°C (AcOEt-Et2O)

NMR (DMSO-d6,δ): 5.39(2H,s), 6.98(1H,d,J=9.7Hz), 7.18(1H,d,J=9.7Hz), 7.20-7.65(10H,m), 8.05(1H,d,J=4.7Hz), 8.90(1H,d,J=4.7Hz), 9.15(1H,s)

IR (nujol): 1664, 1592, 1527 $cm^{-1}$

APCI/MS: 380[M+H]$^+$ .

Example 11

3-(2-Cyclohexyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.

mp: 192-193°C (AcOEt-hexane)

NMR (DMSO-d6,δ): 1.05-1.83(11H,m), 4.75-4.87(1H,m), 6.93(1H,d,J=9.7Hz), 7.25(1H,d,J=9.7Hz), 7.48-7.64(5H,m), 8.09(1H,d,J=4.7Hz), 8.91(1H,dd,J=1.1, 4.7Hz),

9.32(1H,d,J=1.1Hz)
IR (nujol): 1658, 1587, 1521 $cm^{-1}$
APCI/MS: 372[M+H]$^+$
Anal. Calcd for $C_{22}H_{21}N_5O \cdot 0.16H_2O$:
C,70.59; H,5.71; N,18.71
Found: C,70.58; H,5.64 N,18.67.

Example 12

3-(2-Furfuryl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.
mp: 197-201°C (AcOEt-hexane)
NMR (DMSO-d6,δ): 5.40(2H,s), 6.49-6.50(2H,m), 6.95(1H,d,J=9.7Hz), 7.12(1H,d,J=9.7Hz), 7.49-7.68(6H,m), 8.08(1H,d,J=4.7Hz), 8.90(1H,dd,J=1.2, 4.7Hz), 9.23(1H,s)
IR (nujol): 1664, 1592, 1527 $cm^{-1}$
APCI/MS: 370[M+H]$^+$
Anal. Calcd for $C_{21}H_{15}N_5O_2 \cdot 0.37H_2O$:
C,67.07; H,4.22; N,18.62
Found: C,67.06; H,4.01 N,18.58.

Example 13

3-(2-Furan-3-ylmethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.
mp: 157-158°C (AcOEt-hexane)
NMR (DMSO-d6,δ): 5.22(2H,s), 6.50(1H,s), 6.96(1H,d,J=9.7Hz), 7.17(1H,d,J=9.7Hz), 7.48-7.75(7H,m), 8.08(1H,d,J=4.7Hz), 8.90(1H,d,J=4.7Hz), 9.27(1H,s)
IR (nujol): 1660, 1589, 1531 $cm^{-1}$
APCI/MS: 370[M+H]$^+$
Anal. Calcd for $C_{21}H_{15}N_5O_2 \cdot 0.25H_2O$:
C,67.46; H,4.18; N,18.73
Found: C,67.45; H,4.05 N,18.57.

Example 14





3-[2-(2-Thenyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.
mp: 188-189°C (AcOEt-hexane)
NMR (DMSO-d6,δ): 5.55(2H,s), 6.96(1H,d,J=9.7Hz), 7.01-7.06(1H,m), 7.14(1H,d,J=9.7Hz), 7.20-7.21(1H,m), 7.48-7.64(6H,m), 8.09(1H,d, J=4.7Hz), 8.91(1H,dd,J=1.2,4.7Hz), 9.34(1H,d,J=1.2Hz)
IR (nujol): 1660, 1590, 1529 $cm^{-1}$
APCI/MS: 386[M+H]$^+$
Anal. Calcd for $C_{21}H_{15}N_5OS \cdot 0.65H_2O$:
C,63.51; H,4.14; N,17.63
Found: C,63.23; H,3.76 N,17.44.

Example 15

3-[2-(4-Tetrahydropyranyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.
mp: 217-218°C (AcOEt-hexane)
NMR (DMSO-d6,δ): 1.82-1.99(4H,m), 3.43-3.56(2H,m), 3.95-4.01(2H,m), 5.03-5.14(1H,m), 6.96(1H,d,J=9.7Hz), 7.25(1H,d,J=9.7Hz), 7.49-7.65(5H,m), 8.10(1H,d,J=4.7Hz), 8.93(1H,dd,J=1.2, 4.7Hz), 9.34(1H,d,J=1.2Hz)
IR (nujol): 1662, 1589, 1521 $cm^{-1}$
APCI/MS: 374[M+H]$^+$
Anal. Calcd for $C_{21}H_{19}N_5O_2 \cdot 0.27H_2O$:
C,66.68; H,5.21; N,18.51
Found: C,66.67; H,5.06 N,18.44.

Example 16

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(2-methoxyphenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 1.
mp: >250°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 3.55(3H, s), 6.75-6.9(1H, m), 7.0-7.2(2H, m), 7.4-7.7(3H, m), 7.95-8.1(1H, m), 8.8-8.95(1H, m), 9.40(1H, d, J=1.3Hz), 13.1(1H, br)

IR (KBr, $cm^{-1}$): 1679, 1660, 1589

APCI/MS: 320 $[M+H]^+$ .

Example 17

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(2-methoxyphenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 146.0-148.2°C (EtOH)

NMR (DMSO-d6, δ): 1.28(6H, d, J=6.6Hz), 3.50(3H, s), 5.1-5.3(1H, m), 6.88(1H, d, J=9.6Hz), 7.05-7.2(3H, m), 7.45-7.60(2H, m), 8.06(1H, d, J=4.7Hz), 8.89(1H, dd, J=1.3Hz and 4.7Hz), 9.41(1H, d, J=1.2Hz)

IR (KBr, $cm^{-1}$): 1658, 1589

APCI/MS: 362 $[M+H]^+$

Anal $C_{20}H_{19}N_5O_2 \cdot 0.1H_2O$

calcd C:66.14, H:5.33, N:19.28

found C:66.12, H:5.21, N:19.23.

Example 18

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(3-methoxyphenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 1.

mp: 229-230°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 3.78(3H, s), 6.85-7.7(6H, m), 8.07(1H, d, J=4.7Hz), 8.91(1H, dd, J=1.3Hz and 4.7Hz), 9.29(1H, d, J=1.2Hz), 13.3(1H, br)

IR (KBr, $cm^{-1}$): 1677, 1650, 1589

APCI/MS: 320 $[M+H]^+$ .

Example 19

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-methoxyphenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar





manner to that of Example 2.

mp: 165.0-167.1°C (EtOH)

NMR (DMSO-d6, δ): 1.32(6H, d, J=6.6Hz), 3.77(3H, s), 5.1-5.35(1H, m), 6.93(1H, d, J=9.6Hz), 7.0-7.5(5H, m), 8.09(1H, d, J=4.7Hz), 8.92(1H, dd, J=1.3Hz and 4.7Hz), 9.34(1H, d, J=1.3Hz)

IR (KBr, $cm^{-1}$): 1656, 1610, 1587

APCI/MS: 362 $[M+H]^+$

Anal $C_{20}H_{19}N_5O_2 \cdot 0.3H_2O$

calcd C:65.49, H:5.39, N:19.09

found C:65.53, H:5.25, N:19.00.

Example 20

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(4-methoxyphenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 1.

NMR (DMSO-d6, δ): 3.78(3H, s), 6.85-7.8(6H, m), 8.0-8.2(1H, m), 8.9-9.0(1H, m), 9.3-9.4(1H, m), 13.1-13.3(1H, br)

APCI/MS: 320 $[M+H]^+$ .

Example 21

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-methoxyphenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 150.2-153.0°C (EtOH)

NMR (DMSO-d6, δ): 1.32(6H, d, J=6.6Hz), 3.78(3H, s), 5.1-5.3(1H, m), 6.93(1H, d, J=9.6Hz), 7.0-7.6(5H, m), 8.09(1H, d, J=4.8Hz), 8.92(1H, dd, J=1.3Hz and 4.7Hz), 9.34(1H, d, J=1.3Hz)

IR (KBr, $cm^{-1}$): 1656, 1610, 1587

APCI/MS: 362 $[M+H]^+$

Anal $C_{20}H_{19}N_5O_2 \cdot 0.4H_2O$

calcd C:65.17, H:5.41, N:19.00

found C:65.58, H:5.21, N:18.61.

Example 22

To a solution of 3-(2-isopropyl-3-oxo-2,3-

dihydropyridazin-6-yl)-2-(4-methoxyphenyl)pyrazolo[1,5-a]pyrazine (350mg) in dichloromethane (3.0ml) was added a 1N solutoin of boran tribromode in dichloromethane under nitrogen at cooling with a ice-bath. After 1h, the reaction mixture was stirred at ambient temperature for 2h. Water and ethyl acetate were added to the reaction mixture. The separated organic layer was washed with brine and dried over magnesium sulfate. Removal of the solvent in vacuo afforded a 3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-hydroxyphenyl)pyrazolo [1,5-a]pyrazine (152mg)as a pale yellow powder.

mp: 257-260°C (EtOH)

NMR (DMSO-d6, δ): 1.33(6H, d, J=6.6Hz), 5.1-5.35(1H, m), 6.8-7.1(3H, m), 7.1-7.35(2H, m), 7.4-7.5(1H, m), 8.0-8.1(1H, m), 8.9-9.0(1H, m), 9.3-9.4(1H, m)

IR (KBr, $cm^{-1}$): 3127, 1654, 1587

APCI/MS: 348 $[M+H]^+$

Anal $C_{20}H_{19}N_5O_2 \cdot 0.4H_2O$

calcd C:65.17, H:5.41, N:19.00

found C:65.58, H:5.21, N:18.61.

Example 23

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-isopropoxyphenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 108-111°C (diisopropylether)

NMR (DMSO-d6, δ): 1.35(6H, d, J=6.1Hz), 1.50(6H, d, J=6.6Hz), 4.4-4.65(1H, m), 5.3-5.55(1H, m), 6.79(1H, d, J=9.6Hz), 6.95-7.45(5H, m), 8.02(1H, d, J=4.7Hz), 8.43(1H, dd, J=1.4Hz and 4.7Hz), 9.48(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1664, 1594

APCI/MS: 390 $[M+H]^+$

Anal $C_{22}H_{23}N_5O_2$

calcd C:67.85, H:5.95, N:17.98





found C:67.65, H:6.07, N:17.81.

Example 24

To a stirred mixture of 1-aminopyrazium sulfonate (6.6g) and 3-benzenesulfonyl-6-(4-tolylethynyl)pyridazine (3.67g) in N,N,-dimethylformamide (37 ml) was added powder potassium carbonate (7.64 g) at ambient temperature. After stirring 20h, the mixture was poured into water. The resultant precipitate was collected by filtration to give brown powder (4.75 g). A mixture of the obtained powder (4.75 g), sodium hydroxide (2.1 g), water (24 ml) and dioxane (48 ml) was refluxed for 2h. The mixture was acidified with 1N hydrochloric acid. Chloroform was added to the reaction mixture. The separated organic layer was washed with 0.1 N aqueous hydrochloric acid and brine, successively, and dried over magnesium sulfate. The solvent was removed in vacuo. The residue was subjected to column chromatography on silica gel eluting with a mixture of chloroform and methanol (50 : 1) to give 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-tolyl)pyrazolo[1,5-a]pyrazine as a powder (1.0 g)

NMR (DMSO-d6, δ): 2.38(3H, s), 6.89(1H, d, J=9.8Hz), 7.20(1H, d, J=9.8Hz), 7.25-7.40(2H, m), 7.45-7.60(2H, m), 8.05(1H, d, J=4.7Hz), 8.89(1H, dd, J=1.3Hz and 4.7Hz), 9.28(1H, d, J=1.3Hz), 13.28(1H, br)

APCI/MS: 304 $[M+H]^+$ .

Example 25

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-tolyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 112-115°C (diisopropylether)

NMR (DMSO-d6, δ): 1.34(6H, d, J=6.6Hz), 2.38(3H, s), 5.1-5.3(1H, m), 6.92(1H, d, J=9.6Hz), 7.21(1H, d, J=9.6Hz), 7.32(2H, d, J=8.0Hz), 7.52(2H, d, J=8.0Hz), 8.07(1H, d, J=4.7Hz), 8.90(1H, dd, J=1.4Hz and 4.7Hz), 9.32(1H, d, J=1.3Hz)

IR (KBr, $cm^{-1}$): 1664, 1590

APCI/MS: 346 [M+H]$^+$

Anal $C_{20}H_{19}N_5O \cdot 0.3H_2O$

calcd C:68.48, H:5.36, N:19.96

found C:68.29, H:5.45, N:19.69.

Example 26

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-tolyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 207-210°C (EtOH)

NMR (DMSO-d6, δ): 2.38(3H, s), 3.79(3H, s), 6.92(1H, d, J=9.6Hz), 7.14(1H, d, J=9.6Hz), 7.32(2H, d, J=8.0Hz), 7.53(2H, d, J=8.0Hz), 8.07(1H, d, J=4.7Hz), 8.89(1H, dd, J=1.3Hz and 4.7Hz), 9.42(1H, d, J=1.3Hz)

IR (KBr, $cm^{-1}$): 1664, 1587

APCI/MS: 318 [M+H]$^+$

Anal $C_{18}H_{15}N_5O \cdot 0.9H_2O$

calcd C:64.81, H:5.08, N:21.00

found C:65.02, H:4.76, N:20.58.

Example 27

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(4-chlorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 24.

NMR (DMSO-d6, δ): 6.92(1H, d, J=9.8Hz), 7.28(1H, d, J=9.8Hz), 7.5-7.7(4H, m), 8.08(1H, d, J=4.7Hz), 8.90(1H, dd, J=1.3Hz and 4.7Hz), 9.29(1H, d, J=1.3Hz), 13.29(1H, br)

IR (KBr, $cm^{-1}$): 1671, 1648, 1596

APCI/MS: 324 [M+H]$^+$.

Example 28

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-chlorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.





mp: 167-169°C (EtOH)

NMR (DMSO-d6, δ): 1.30(6H, d, J=6.6Hz), 5.1-5.3(1H, m), 6.95(1H, d, J=9.6Hz), 7.33(1H, d, J=9.6Hz), 7.5-7.7(4H, m), 8.10(1H, d, J=4.7Hz), 8.92(1H, dd, J=1.4Hz and 4.7Hz), 9.33(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1668, 1594

APCI/MS: 366 [M+H]$^+$

Anal $C_{20}H_{19}N_5O_2 \cdot 0.4H_2O$

calcd C:62.38, H:4.41, N:19.14

found C:62.32, H:4.33, N:19.07.

Example 29

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(3-chlorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 1.

mp: >250°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 6.93(1H, d, J=9.8Hz), 7.30(1H, d, J=9.8Hz), 7.5-7.75(4H, m), 8.0-8.2(1H, m), 8.8-8.95(1H, m), 9.2-9.4(1H, m), 13.32(1H, br)

IR (KBr, $cm^{-1}$): 1675, 1648, 1596

APCI/MS: 324 [M+H]$^+$.

Example 30

To a stirred solution of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-chlorophenyl)pyrazolo[1,5-a]pyrazine (400 mg) in N,N-dimethylformamide (6 ml) was added 60%-sodium hydroxide (74 mg) at ambient temperature. After stirring for 1 h, isopropyl iodide (0.25 ml) was added to the mixture which was stirred 16 hours. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporater in vacuo. The residue was recrystallized from a ethyl acetate to give 3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-chlorophenyl)pyrazolo [1,5-a]pyrazine (330 mg) as a pale yellow solid.

mp: 195-197°C (AcOEt)

NMR (DMSO-d6, δ): 1.27(6H, d, J=6.6Hz), 5.1-5.25(1H, m), 6.97(1H, d, J=9.6Hz), 7.41(1H, d, J=9.6Hz), 7.45-7.7(4H, m), 8.11(1H, d, J=4.7Hz), 8.93(1H, dd, J=1.3Hz and 4.7Hz), 9.34(1H, d, J=1.3Hz)
IR (KBr, $cm^{-1}$): 1673, 1670, 1664, 1650, 1600, 1594
APCI/MS: 366 [M+H]$^+$
Anal $C_{19}H_{16}N_5O \cdot 0.2H_2O$
calcd C:61.77, H:4.47, N:18.96
found C:61.69, H:4.27, N:18.94.

Example 31

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-chlorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.
mp: 239-241°C (AcOEt)
NMR (DMSO-d6, δ): 3.78(3H, s), 6.95(1H, d, J=9.6Hz), 7.24(1H, d, J=9.6Hz), 7.5-7.65(3H, m), 7.7-7.8(1H, m), 8.11(1H, d, J=4.7Hz), 8.92(1H, dd, J=1.4Hz and 4.7Hz), 9.44(1H, d, J=1.4Hz)
IR (KBr, $cm^{-1}$): 1658, 1587
APCI/MS: 338 [M+H]$^+$
Anal $C_{17}H_{12}ClN_5O$
calcd C:60.45, H:3.58, N:20.73
found C:60.21, H:3.58, N:20.66.

Example 32

3-[2-(3-Tetrahydrofuranyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-(3-chlorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.
mp: 190-192°C (EtOH)
NMR (DMSO-d6, δ): 2.0-2.6(2H, m), 3.7-4.1(4H, m), 5.5-5.7(1H, m), 6.97(1H, d, J=9.6Hz), 7.34(1H, d, J=9.6Hz), 7.5-7.6(3H, m), 7.65-7.75(1H, m), 8.11(1H, d, J=4.7Hz), 8.92(1H, dd, J=1.3Hz and 4.7Hz), 9.39(1H, d, J=1.1Hz)
IR (KBr, $cm^{-1}$): 1662, 1587
APCI/MS: 394 [M+H]$^+$





Anal $C_{20}H_{16}ClN_5O_2 \cdot 0.1H_2O$
calcd C:60.72, H:4.13, N:17.70
found C:60.56, H:3.96, N:17.67.

Example 33

3-[2-(4-Tetrahydropyranyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-(3-chlorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.
mp: 153-155°C (EtOH)
NMR (DMSO-d6, δ): 1.7-1.9(4H, m), 3.4-3.6(2H, m), 3.85-4.0(2H, m), 4.95-5.2(1H, m), 7.00(1H, d, J=9.6Hz), 7.41(1H, d, J=9.6Hz), 7.45-7.6(3H, m), 7.65-7.70(1H, m), 8.12(1H, d, J=4.7Hz), 8.9-9.0(1H, m), 9.3-9.4(1H, m)
IR (KBr, $cm^{-1}$): 1664, 1662, 1592
APCI/MS: 408 [M+H]$^+$
Anal $C_{21}H_{18}ClN_5O_2 \cdot 0.5H_2O$
calcd C:60.57, H:4.59, N:16.80
found C:60.71, H:4.55, N:16.42.

Example 34

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(2-chlorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 24.
mp: >250°C ($CHCl_3$, MeOH)
NMR (DMSO-d6, δ): 6.86(1H, d, J=9.9Hz), 7.04(1H, d, J=9.9Hz), 7.45-7.75(4H, m), 8.12(1H, d, J=4.7Hz), 8.93(1H, dd, J=1.3Hz and 4.7Hz), 9.47(1H, m), 13.23(1H, br)
IR (KBr, $cm^{-1}$): 1685, 1662, 1592
APCI/MS: 324 [M+H]$^+$.

Example 35

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(2-chlorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.
mp: 142-144°C (EtOH)

NMR (DMSO-d6, δ): 1.12(6H, d, J=6.6Hz), 5.0-5.2(1H, m), 6.96(1H, d, J=9.6Hz), 7.36(1H, d, J=9.6Hz), 7.45-7.7(4H, m), 8.13(1H, d, J=4.7Hz), 8.94(1H, d, J= 4.3Hz), 9.50(1H, s)

IR (KBr, $cm^{-1}$): 1660, 1590

APCI/MS: 366 $[M+H]^+$

Anal $C_{19}H_{16}ClN_5O \cdot 0.3H_2O$

calcd C:61.47, H:4.51, N:18.87

found C:61.54, H:4.33, N:18.76.

Example 36

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(2-fluorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 1.

mp: >250°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 6.90(1H, d, J=9.8Hz), 7.25(1H, d, J=9.8Hz), 7.3-7.45(2H, m), 7.5-7.75(2H, m), 8.11(1H, d, J=4.7Hz), 8.93(1H, dd, J=1.4Hz and 4.7Hz), 9.39(1H, d, J=1.4Hz), 13.2(1H, br)

IR (KBr, $cm^{-1}$): 1689, 1668, 1592

APCI/MS: 308 $[M+H]^+$.

Example 37

To a stirred solution of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-(2-fluorophenyl) pyrazolo[1,5-a]pyrazine (20.1 g) in N,N-dimethylformamide (180 ml) was added 60%-sodium hydroxide (3.92 g) at ambient temperature. After stirring for 1 hour, isopropyl iodide (13.0 ml) was added to the mixture which was stirred 16 hours. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporater in vacuo. The residue was recrystallized from a ethanol to give 3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(2-fluorophenyl)pyrazolo [1,5-a]pyrazine (18.1 g) as a pale yellow solid.

mp: 180-181°C (EtOH)

NMR (DMSO-d6, δ): 1.17(6H, d, J=6.6Hz), 5.0-5.25(1H, m), 6.95(1H,





d, J=9.6Hz), 7.2-7.8(5H, m), 8.12(1H, d, J=4.7Hz), 8.94(1H, dd, J= 1.4Hz and 4.7Hz), 9.43(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1662, 1590

APCI/MS: 350 $[M+H]^+$

Anal $C_{19}H_{16}FN_5O$

calcd C:65.32, H:4.62, N:20.05

found C:65.15, H:4.51, N:20.01.

Example 38

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 1.

mp: >250°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 6.91(1H, d, J=9.8Hz), 7.2-7.7(5H, m), 8.0-8.15(1H, m), 8.8-8.95(1H, m), 9.2-9.4(1H, m),13.3(1H, br)

IR (KBr, $cm^{-1}$): 1685, 1652, 1598

APCI/MS: 308 $[M+H]^+$.

Example 39

To a stirred solution of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluorophenyl)pyrazolo[1,5-a]pyrazine (400 mg) in N,N-dimethylformamide (5 ml) was added 60%-sodium hydroxide (78 mg) at ambient temperature. After stirring for 1 h, isopropyl iodide (0.26 ml) was added to the mixture which was stirred 16 hours. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporater in vacuo. The residue was recrystallized from a ethanol to give 3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluorophenyl)pyrazolo[1,5-a]pyrazine (250 mg) as a pale yellow solid.

mp: 155-157°C (EtOH)

NMR (DMSO-d6, δ): 1.28(6H, d, J=6.6Hz), 5.1-5.3(1H, m), 6.96(1H, d, J=9.6Hz), 7.37(1H, d, J=9.6Hz), 7.3-7.65(4H, m), 8.11(1H, d, J=4.7Hz), 8.93(1H, dd, J= 1.4Hz and 4.7Hz), 9.34(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1664, 1658, 1612, 1590

APCI/MS: 350 $[M+H]^+$

Anal $C_{19}H_{16}FN_5O$

calcd C:65.32, H:4.62, N:20.05

found C:65.38, H:4.65, N:19.97.

Example 40

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(4-fluorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 1.

mp: >250°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ):6.91(1H, d, J=9.8Hz), 7.25(1H, d, J=9.8Hz), 7.2-7.45(2H, m), 7.6-7.75(2H, m), 8.07(1H, d, J=4.7Hz), 8.90(1H, dd, J=1.4Hz and 4.7Hz), 9.29(1H, d, J=1.4Hz), 13.29(1H, br)

IR (KBr, $cm^{-1}$): 1675, 1650, 1598

APCI/MS: 308 $[M+H]^+$ .

Example 41

To a stirred solution of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-fluorophenyl)pyrazolo[1,5-a]pyrazine (15.0 g) in N,N-dimethylformamide (200 ml) was added 60%-sodium hydroxide (2.93 g) at ambient temperature. After stirring for 1 h, isopropyl iodide (9.7 ml) was added to the mixture which was stirred 16 hours. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporater in vacuo. The residue was recrystallized from a ethanol to give 3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-fluorophenyl)pyrazolo[1,5-a]pyrazine (13.6 g) as a pale yellow solid.

mp: 196-197°C (EtOH)

NMR (DMSO-d6, δ): 1.29(6H, d, J=6.6Hz), 5.1-5.3(1H, m), 6.94(1H, d, J=9.6Hz), 7.25-7.45(3H, m), 7.6-7.8(2H, m), 8.09(1H, d, J=4.7Hz), 8.91(1H, dd, J= 1.4Hz and 4.7Hz), 9.33(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1671, 1662, 1600, 1594





APCI/MS: 350 $[M+H]^+$

Anal $C_{19}H_{16}FN_5O$

calcd C:65.32, H:4.62, N:20.05

found C:65.48, H:4.60, N:20.10.

Example 42

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-fluorophenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 235-237°C (EtOH)

NMR (DMSO-d6, δ):3.78(3H, s), 6.94(1H, d, J=9.6Hz), 7.18(1H, d, J=9.6Hz), 7.25-7.45(2H, m), 7.6-7.75(2H, m), 8.09(1H, d, J=4.7Hz), 8.90(1H, dd, J= 1.3Hz and 4.7Hz), 9.43(1H, d, J=1.3Hz)

IR (KBr, $cm^{-1}$): 1679, 1608, 1590

APCI/MS: 322 $[M+H]^+$

Anal $C_{17}H_{12}FN_5O \cdot 0.1H_2O$

calcd C:63.19, H:3.81, N:21.67

found C:63.11, H:3.68, N:21.64.

Example 43

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-chlorophenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 236-238°C (EtOH)

NMR (DMSO-d6, δ): 3.78(3H, s), 6.95(1H, d, J=9.6Hz), 7.21(1H, d, J=9.6Hz), 7.57(2H, d, J=8.5Hz), 7.68(2H, d, J=8.5Hz), 8.10(1H, d, J=4.7Hz), 8.88-8.20(1H, m), 9.43(1H, br)

IR (KBr, $cm^{-1}$): 1677, 1589

APCI/MS: 338 $[M+H]^+$

Anal $C_{17}H_{12}ClN_5O$

calcd C:60.45, H:3.58, N:20.73

found C:60.19, H:3.50, N:20.64.

Example 44

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(4-pentylphenyl)

pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 24.

mp: 231-234°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 0.8-0.95(3H, m), 1.2-1.45(4H, m), 1.5-1.7(2H, m), 2.55-2.75(2H, m), 6.89(1H, d, J=9.8Hz), 7.21(1H, d, J=9.8Hz), 7.31(2H, d, J=8.1Hz), 7.53(2H, d, J=8.1Hz), 8.05(1H, d, J=4.7Hz), 8.88(1H, dd, J=1.4Hz and 4.7Hz), 9.27(1H, m), 13.27(1H, br)

IR (KBr, $cm^{-1}$): 1675, 1656, 1592

APCI/MS: 360 $[M+H]^+$

Example 45

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-pentylphenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 127-128°C (diisopropylether)

NMR (DMSO-d6, δ): 0.80-0.93(3H, m), 1.2-1.45(10H, m), 1.5-1.7(2H, m), 2.55-2.70(2H, m), 5.1-5.3(1H, m), 6.92(1H, d, J=9.6Hz), 7.27(1H, d, J=9.6Hz), 7.29-7.4(2H, m), 7.52(1H, d, J=8.1Hz), 8.07(1H, d, J=4.7Hz), 8.90(1H, dd, J=1.3Hz and 4.7Hz), 9.31(1H, d, J=1.1Hz)

IR (KBr, $cm^{-1}$): 1664, 1590

APCI/MS: 402 $[M+H]^+$

Anal $C_{24}H_{27}N_5O \cdot 0.2H_2O$

calcd C:71.16, H:6.82, N:17.29

found C:71.49, H:6.85, N:16.99.

Example 46

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(4-pentylphenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 150-152°C (diisopropylether)

NMR (DMSO-d6, δ): 0.8-0.95(3H, m), 1.25-1.4(4H, m), 1.5-1.7(2H, m), 2.55-2.7(2H, m), 3.79(3H, s), 6.92(1H, d, J=9.6Hz), 7.15(1H, d, J=9.6Hz), 7.32(2H, d, J=8.1Hz), 7.54(2H, d, J=8.1Hz), 8.07(1H,





d, J=4.7Hz), 8.88(1H, dd, J=1.3Hz and 4.7Hz), 9.41(1H, d, J=1.3Hz)

IR (KBr, $cm^{-1}$): 1662, 1617, 1589

APCI/MS: 374 $[M+H]^+$

Anal $C_{22}H_{23}N_5O \cdot 0.2H_2O$

calcd C:70.08, H:6.25, N:18.57

found C:70.08, H:6.17, N:18.51.

Example 47

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(2-fluorophenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 185-187°C (EtOH)

NMR (DMSO-d6, δ): 3.74(3H, s), 6.93(1H, d, J=9.6Hz), 7.15(1H, d, J=9.6Hz), 7.3-7.45(2H, m), 7.5-7.75(2H, m), 8.13(1H, d, J=4.7Hz), 8.94(1H, dd, J=1.4Hz and 4.7Hz), 9.54(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1679, 1670, 1594, 1590

APCI/MS: 322 $[M+H]^+$.

Example 48

3-(2-Methyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluorophenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 194-195°C (EtOH)

NMR (DMSO-d6, δ): 3.88(3H, s), 6.96(1H, d, J=9.6Hz), 7.21(1H, d, J=9.6Hz), 7.25-7.65(4H, m), 8.10(1H, d, J=4.7Hz), 8.91(1H, dd, J=1.4Hz and 4.7Hz), 9.44(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1673, 1616, 1587

APCI/MS: 322 $[M+H]^+$.

Example 49

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(3,4-difluorophenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 1.

mp: >250°C ($CHCl_3$, MeOH)

NMR (DMSO-d6, δ): 6.92(1H, d, J=9.8Hz), 7.32(1H, d, J=9.8Hz),

7.4-7.8(4H, m), 8.11(1H, d, J=4.8Hz), 8.94(1H, dd, J+1.4Hz and 4.8Hz), 9.33(1H, d, J=1.4Hz), 13.2-13.5(1H, br)
IR (KBr, $cm^{-1}$): 1671, 1648, 1594
APCI/MS: 326 $[M+H]^+$.

Example 50

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3,4-difluorophenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.
mp: 175-176°C (EtOH)
NMR (DMSO-d6, δ): 1.28(6H, d, J=6.6Hz), 5.05-5.3(1H, m), 6.96(1H, d, J=9.6Hz), 7.40(1H, d, J=9.6Hz), 7.4-7.8(3H, m), 8.11(1H, d, J=4.7Hz), 8.92(1H, dd, J= 1.4Hz and 4.7Hz), 9.34(1H, d, J=1.4Hz)
IR (KBr, $cm^{-1}$): 1662, 1590
APCI/MS: 368 $[M+H]^+$
Anal $C_{19}H_{16}F_2N_5O$
calcd C:61.82, H:4.15, N:18.97
found C:61.77, H:4.10, N:18.84.

Example 51

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(2,4-difluorophenyl)pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 1.
mp: >250°C ($CHCl_3$, MeOH)
NMR (DMSO-d6, δ):6.91(1H, d, J=9.8Hz), 7.2-7.8(4H, m), 8.11(1H, d, J=4.8Hz), 8.93(1H, dd, J=1.4Hz and 4.7Hz), 9.39(1H, d, J=1.4Hz), 13.22(1H, br)
IR (KBr, $cm^{-1}$): 1691, 1670, 1621, 1592
APCI/MS: 326 $[M+H]^+$.

Example 52

To a stirred solution of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-(2,4-difluorophenyl)pyrazolo[1,5-a]pyrazine (460 mg) in N,N-dimethylformamide (5 ml) was added 60%-sodium hydroxide (85 mg) at ambient temperature. After stirring for 1 h, isopropyl





iodide (0.25 ml) was added to the mixture which was stirred 16 hours. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporater in vacuo. The residue was recrystallized from a ethanol to give 3-(2-isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(2,4-difluorophenyl)pyrazolo[1,5-a]pyrazine (195 mg) as a pale yellow solid.
mp: 165-166°C (EtOH)
NMR (DMSO-d6, δ): 1.17(6H, d, J=6.6Hz), 5.0-5.3(1H, m), 6.97(1H, d, J=9.6Hz), 7.2-7.55(3H, m), 7.65-7.85(1H, m), 8.12(1H, d, J=4.7Hz), 8.94(1H, dd, J= 1.4Hz and 4.7Hz), 9.43(1H, d, J=1.4Hz)
IR (KBr, $cm^{-1}$): 1666, 1619, 1592
APCI/MS: 368 $[M+H]^+$
Anal $C_{19}H_{15}F_2N_5O \cdot 0.1H_2O$
calcd C:61.82, H:4.15, N:18.97
found C:61.71, H:4.05, N:18.85.

Example 53

3-[2-(3-Tetrahydrofuranyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-(4-fluorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.
mp: 202.1-203.5°C (EtOH)
NMR (DMSO-d6, δ): 2.0-2.5(2H, m), 3.7-4.1(4H, m), 5.5-5.7(1H, m), 6.95(1H, d, J=9.6Hz), 7.26(1H, d, J=9.6Hz), 7.3-7.5(2H, m), 7.6-7.8(2H, m), 8.09(1H, d, J=4.7Hz), 8.90(1H, dd, J=1.4Hz and 4.7Hz), 9.38(1H, d, J=1.4Hz)
IR (KBr, $cm^{-1}$): 1658, 1585
APCI/MS: 378 $[M+H]^+$
Anal $C_{20}H_{16}FN_5O_2 \cdot 0.1H_2O$
calcd C:63.35, H:4.31, N:18.47
found C:63.29, H:4.18, N:18.46.

Example 54

3-[2-(4-Tetrahydropyranyl)-3-oxo-2,3-dihydropyridazin-6-

yl]-2-(4-fluorophenyl) pyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.

mp: 209-211°C (EtOH)

NMR (DMSO-d6, δ): 1.7-2.0(4H, m), 3.35-3.6(2H, m), 3.85-4.05(2H, m), 4.95-5.2(1H, m), 6.97(1H, d, J=9.6Hz), 7.29(1H, d, J=9.6Hz), 7.25-7.45(2H, m), 7.6-7.75(2H, m), 8.05-8.15(1H, m), 8.92(1H, dd, J=1.4Hz and 4.7Hz), 9.32(1H, d, J=1.4Hz)

IR (KBr, $cm^{-1}$): 1670, 1596

APCI/MS: 392 $[M+H]^+$

Anal $C_{21}H_{18}FN_5O_2 \cdot 0.3H_2O$

calcd C:63.56, H:4.72, N:17.65

found C:63.45, H:4.68, N:17.62.

Example 55

3-(2-Cyanomethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp:195-200°C (AcOEt-Hexane)

NMR(DMSO, δ): 5.41(2H,S), 7.03(1H,d,J=9.7Hz), 7.18(1H,d,J=9.7Hz), 7.51-7.70(5H,m), 8.13(1H,d,J=4.7Hz), 8.94(1H,d,J=1.3,4.7Hz), 9.55(1H,d,J=1.3Hz)

IR(nujol):1677, 1600, 1527 $cm^{-1}$

ESI/MS: 351 $[M+Na]^+$

Anal. Calcd for $C_{18}H_{12}N_6O \cdot 0.17AcOEt$:

C,65.35; H,3.92; N,24.48.

Found: C, 65.09; H, 3.67; N, 24.74.

Example 56

A mixture of 3-(2-thiocarbamoylmethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (1g) and bromoacetaldehyde dimethyl acetal(0.85ml) in dimethoxyethane (20ml) was refluxed for one day. After evaporating the solvent, the residue was partitioned between chloroform and an aquous sodium bicarbonate. The separated





organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (150ml) using ethyl acetate. The desired fractions were collected and evaporated in vacuo. The residue was recrystallized from ethyl acetate to give 3-[2-(1,3-thiazol-2-ylmethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine (0.49g).

mp: 196-198°C (EtOAc)

NMR(DMSO, δ): 5.72(2H,S), 7.01(1H,d,J=9.7Hz), 7.18(1H,d,J=9.7Hz), 7.49-7.53(3H,m), 7.62-7.67(2H,m), 7.76(1H,d,J=3.3Hz), 7.83(1H,d,J=3.3Hz), 8.09(1H,d,J=9.7Hz), 8.92(1H,dd,J=1.3,4.7Hz), 9.33(1H,d,J=1.3Hz)

IR(nujol): 1662, 1590, 1527, 1500 $cm^{-1}$

APCI/MS: 387 $[M+H]^+$

Anal. Calcd for $C_{18}H_{12}N_6O \cdot 0.2H_2O$:

C,61.59; H,3.72; N,21.55.

Found: C, 61.78; H, 3.54; N, 21.50.

Example 57

To a solution of 3-[2-(1-tert-butoxycarbonylpiperidin-4-yl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine (2.2g) in ethyl acetate(50ml) was added 4N-hydrogen chloride in ethyl acetate(17ml) at ambient temperature. After stirring for 18hours, the solvent were evaporated in vacuo. The residue was partitioned between water sodium bicarbonate and ethyl acetate. The separated water layer was made basic with an aqueous sodium bicarbonate and extracted with chloroform. The separated organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 3-(2-piperidin-4-yl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (1.67g) as a yellow solid.

mp: 210-212°C (EtOAc)

NMR(DMSO, δ): 1.70-1.85(4H,m), 2.50-2.67(2H,m), 3.02-3.10(2H,m), 4.80-5.00(1H,m), 4.97-5.10(1H,m), 6.93(1H,d,J=9.7Hz), 7.20(1H,d,J=9.7Hz), 7.50-7.65(5H,m), 8.09(1H,d,J=4.7Hz), 8.92(1H,dd,J=1.3,4.7Hz), 9.34(1H,d,J=1.3Hz).

APCI/MS: 373 $[M+H]^+$

IR(nujol): 3529, 3293, 1668, 1589, 1521 $cm^{-1}$

Anal. Calcd for $C_{21}H_{20}N_6 \cdot 1H_2O \cdot 0.2AcOEt$:

C,64.17; H,5.83; N,20.59.

Found: C,64.00; H,5.61; N,20.63.

Example 58

3-(2-Tetrahydrofuran-3-yl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 3.

mp: 175-176°C (EtOAc-Hexane)

NMR(DMSO, δ): 2.16-2.24(2H,m), 3.72-4.05(4H,m), 5.57-5.64(1H,m), 6.93(1H,d,J=9.6Hz), 7.21(1H,d,J=9.6Hz), 7.49-7.66(5H,m), 8.09(1H,d,J=4.7Hz), 8.91(1H,dd,J=1.2,4.7Hz), 9.39(1H,d,J=1.2Hz)

IR(nujol): 1662, 1590, 1517 $cm^{-1}$

APCI/MS: 360 $[M+H]^+$

Anal. Calcd for $C_{20}H_{17}N_5O_2 \cdot 0.3H_2O$:

C,65.85; H,4.86; N,19.20.

Found: C,65.82; H,4.62; N,19.00.

Example 59

(R)-3-[2-(3R)-Tetrahydrofuran-3-yl-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 2.

mp: 180-182°C (EtOH)

$[\alpha]_D$=86.4°(C=0.25, EtOH, 22°C)

IR(nujol): 1662, 1589, 1517 $cm^{-1}$

Anal. Calcd for $C_{20}H_{17}N_5O_2$:

C,66.84; H,4.77; N,19.49.





Found: C,66.73; H,4.65; N,19.43.

Example 60

(S)-3-[2-(3S)-Tetrahydrofuran-3-yl-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that carried out in the preparation of Example 2.

mp: 180-181°C (AtOAc)

$[\alpha]_D$=82.4°(C=0.25, EtOH, 28°C)

IR(nujol): 1662, 1590, 1519 $cm^{-1}$

Anal. Calcd for $C_{20}H_{17}N_5O_2$:

C,66.84; H,4.77; N,19.49.

Found: C,66.59; H,4.65; N,19.34.

Example 61

To a suspension of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (200 mg) in dimethylformamide (4 ml) was added sodium hydride (60% oil suspension, 41.5 mg) and stirred at room temperature for 10 min. To the mixture was added 1-bromo-3-fluoropropane (0.095 ml) and stirred at room temperature for 16 hours. The reaction mixture was poured into ice water, extracted with EtOAc, washed with water and brine, dried over sodium sulfate, evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc) to give 3-[2-(3-fluoropropyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine (139.5 mg) as a solid.

mp: 154-155°C (EtOAc-hexane)

1H NMR (CDCl3, δ): 2.20-2.50 (2H,m), 4.40-4.80 (4H, m), 6.81 (1H, d, J = 9.7 Hz), 7.06 (1H, d, J = 9.7 Hz), 7.45-7.70 (5H, m), 8.04 (1H, d, J = 4.7 Hz), 8.44 (1H, dd, J = 4.7, 1.4 Hz), 9.47 (1H, d, J = 1.4 Hz)

IR (KBr): 3026, 2970, 1662, 1587, 1504, 1311 $cm^{-1}$

APCI/MS: 350 $[M+H]^+$.

Example 62

3-[2-(3,3,3-Trifluoropropyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 61.

mp: 156-157°C (Et2O-hexane)

1H NMR (CDCl3, δ): 2.65-2.93 (2H,m), 4.55 (2H, t, J = 7.0 Hz), 6.82 (1H, d, J = 9.7 Hz), 7.07 (1H, d, J = 9.7 Hz), 7.43-7.68 (5H, m), 8.05 (1H, d, J = 4.7 Hz), 8.44 (1H, dd, J = 4.7, 1.4 Hz), 9.43 (1H, d, J = 1.4 Hz)

IR (KBr): 3087, 3024, 2960, 1668, 1591, 1522, 1502, 1460 $cm^{-1}$

APCI/MS: 386 $[M+H]^+$ .

Example 63

To a suspension of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine (200 mg) in dimethylformamide (4 ml) was added sodium hydride (60% oil suspension, 41.5 mg) and stirred at room temperature for 10 minutes. To the mixture was added 2-iodo-1,1,1-trifluoroethane (0.682 ml) and stirred at 60°C for 15 hours. To the mixture was added another 2-iodo-1,1,1-trifluoroethane (0.682 ml) and stirred at 60°C for 24 hours. After cooling to room temperature, the reaction mixture was poured into ice water, extracted with EtOAc, washed with water and brine, dried over sodium sulfate, evaporated in vacuo. The residue was purified by silica gel column chromatography ($CH_2Cl_2$-MeOH, 30:1) to give 3-[2-(2,2,2-trifluoroethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine (138.3 mg) as a solid.

mp: 208-209°C ($Et_2O$-hexane)

1H NMR (CDCl3, δ): 4.92 (2H, q, J = 8.4 Hz), 6.84 (1H, d, J = 9.8 Hz), 7.07 (1H, d, J = 9.8 Hz), 7.43-7.67 (5H, m), 8.06 (1H, d, J = 4.7 Hz), 8.44 (1H, dd, J = 4.7, 1.3 Hz), 9.46 (1H, d, J = 1.3 Hz)

IR (KBr): 3072, 3028, 1676, 1599, 1525, 1508, 1460 $cm^{-1}$

APCI/MS: 372 $[M+H]^+$ .





Example 64

3-(2-Isobutyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine was obtained in a similar manner to that of Example 61.

mp: 150-151°C (EtOAc-hexane)

1H NMR (CDCl3, δ): 1.04 (6H, d, J = 6.7 Hz), 2.27-2.55 (1H, m), 4.12 (2H, d, J = 7.5 Hz), 6.80 (1H, d, J = 9.7 Hz), 7.03 (1H, d, J = 9.7 Hz), 7.38-7.68 (5H, m), 8.02 (1H, d, J = 4.7 Hz), 8.43 (1H, dd, J = 4.7, 1.4 Hz), 9.46 (1H, d, J = 1.4 Hz)

IR (KBr): 3068, 3026, 2960, 2868, 1670, 1592, 1527, 1504, 1460 $cm^{-1}$

APCI/MS: 346 $[M+H]^+$ .

Example 65

The following compounds were obtained in a similar manner to that of Example 61.

1) 3-[2-(2-Fluoroethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyrazine

mp: 167-168°C (EtOAc-hexane)

1H NMR (CDCl3, δ): 4.50-5.08 (4H,m), 6.83 (1H, d, J = 9.7 Hz), 7.08 (1H, d, J = 9.7 Hz), 7.43-7.68 (5H, m), 8.03 (1H, d, J = 4.7 Hz), 8.43 (1H, dd, J = 4.7, 1.4 Hz), 9.48 (1H, d, J = 1.4 Hz)

IR (KBr): 3095, 3028, 2954, 1668, 1591, 1522, 1504, 1456 $cm^{-1}$

APCI/MS: 336 $[M+H]^+$

2) 3-(2-Vinyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyrazine

mp: 191-193°C (EtOAc-hexane)

1H NMR (CDCl3, δ): 5.11 (1H, d, J = 8.8 Hz), 5.91 (1H, d, J = 15.5 Hz), 6.83 (1H, d, J = 9.8 Hz), 7.04 (1H, d, J = 9.8 Hz), 7.43-7.70 (5H, m), 7.86 (1H, dd, J = 15.5, 8.8 Hz), 8.06 (1H, d, J = 4.7 Hz), 8.45 (1H, dd, J = 4.7, 1.4 Hz), 9.54 (1H, d, J = 1.4 Hz)

IR (KBr): 3089, 1660, 1637, 1527, 1462 $cm^{-1}$

APCI/MS: 316 $[M+H]^+$ .

Example 66

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(5-fluoro-2-methoxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Example 1.

Example 67

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(5-fluoro-2-methoxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Example 2.

Example 68

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(5-fluoro-2-hydroxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Example 22.

Example 69

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluoro-5-methoxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Example 1.

Example 70

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluoro-5-methoxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Example 2.

Example 71

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluoro-5-hydroxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Example 22.

Example 72

3-(3-Oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Example 1.

Example 73

3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Example 2.

Example 74

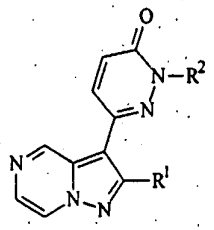




3-(2-Isopropyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-(3-fluoro-4-hydroxyphenyl)pyrazolo[1,5-a]pyrazine can be obtained in a similar manner to that of Example 22.

CLAIMS

1. A pyrazolopyrazine compound of the following formula (I):



(I)

wherein

$R^1$ is aryl which may have one or more suitable substituent(s); and

$R^2$ is hydrogen;
lower alkyl;
lower alkenyl;
cyclo(lower)alkyl;
heteromonocyclic group; or
lower alkyl substituted with one or more substituent(s) selected from the group consisting of cyclo(lower)alkyl, halogen, cyano, aryl and heteromonocyclic group,
or a salt thereof.

2. A compound of claim 1,
wherein
$R^1$ is phenyl which may have one or more substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, hydroxy and halogen; and
$R^2$ is hydrogen;
lower alkyl;
lower alkenyl;
mono- or di- or trihalo(lower)alkyl;
cyclo(C3-C8)alkyl;
3 to 8-membered heteromonocyclic group; or





lower alkyl substituted with a substituent selected from the group consisting of cyclo(C3-C8)alkyl, cyano, phenyl and 3 to 8-membered heteromonocyclic group.

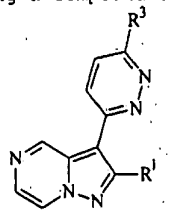
3. A compound of claim 2,
wherein
$R^1$ is phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, hydroxy and halogen; and
$R^2$ is hydrogen;
lower alkyl;
lower alkenyl;
mono- or di- or trihalo(lower)alkyl;
cyclo(C3-C8)alkyl;
3 to 8-membered heteromonocyclic group containing 1 to 4 hetero atom(s) selected from among oxygen, sulfur and nitrogen in its ring; or
lower alkyl substituted with a substituent selected from the group consisting of cyclo(C3-C8)alkyl, cyano, phenyl and 3 to 8-membered heteromonocyclic group containing 1 to 4 hetero atom(s) selected from among oxygen, sulfur and nitrogen in its ring.

4. A compound of claim 3,
wherein
$R^2$ is hydrogen;
lower alkyl;
lower alkenyl;
mono- or di- or trihalo(lower)alkyl;
cyclo(C3-C8)alkyl;
saturated 5 to 6-memberd heteromonocyclic group containing 1 to 2 oxygen atom(s) in its ring;
unsaturated 5 to 6-membered heteromonocyclic group containing 1

to 2 hetero atom(s) selected from among oxygen, sulfur and nitrogen in its ring; or
lower alkyl substituted with a substituent selected from the group consisting of cyclo(C3-C8)alkyl, cyano, phenyl, saturated 5 to 6-memberd heteromonocyclic group containing 1 to 2 oxygen atom(s) in its ring and unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 hetero atom(s) selected from among oxygen, sulfur and nitrogen in its ring.

5. A compound of claim 4,
wherein
$R^2$ is hydrogen;
lower alkyl;
lower alkenyl;
fluoro(lower)alkyl;
trifluoro(lower)alkyl;
cyclo(C3-C8)alkyl;
heteromonocyclic group selected from the group consisting of tetrahydrofuranyl, tetrahydropyranyl, pyridyl, furanyl, thienyl and thiazolyl; or
lower alkyl substituted with a substituent selected from the group consisting of cyclo(C3-C8)alkyl, cyano, phenyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, furanyl, thienyl and thiazolyl.

6. A process for the preparation of the pyrazolopyrazine compound of claim 1 or a salt thereof, which comprises,
(1) hydrolyzing a compound of the formula (II):

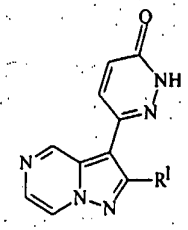


(II)





wherein $R^1$ is aryl which may have one or more suitable substituent(s);
$R^3$ is arylsulfonyl which may have one or more suitable substituent(s);
di(lower)alkylamino;
lower alkoxy;
lower alkylthio; or
acyloxy,
or a salt thereof,
to give a compound of the formula (Ia):

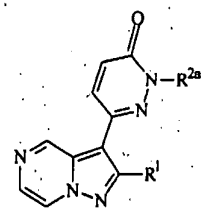


(Ia)

wherein $R^1$ is as defined above or a salt thereof,
(2) reacting a compound of the formula (Ia) or a salt thereof, with a compound of the formula (III):

$R^{2a}$-X (III)

wherein $R^{2a}$ is lower alkyl;
cyclo(lower)alkyl;
lower alkyl substituted with cyclo(lower)alkyl;
lower alkyl substituted with aryl;
heteromonocyclic group; or
lower alkyl substituted with heteromonocyclic group, and
X is a leaving group,
or a salt thereof
to give a compound of the formula (Ib):

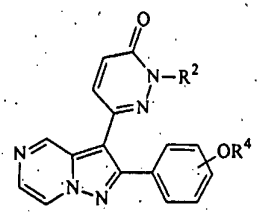


(Ib)

wherein $R^1$, $R^{2a}$ are as defined above,

or a salt thereof,

(3) eliminating of alkyl group of a compound of the formula (Ic):



(Ic)

wherein $R^2$ is hydrogen;

lower alkyl;

cyclo(lower)alkyl;

lower alkyl substituted with cyclo(lower)alkyl;

lower alkyl substituted with aryl;

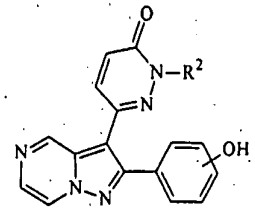
heteromonocyclic group; or

lower alkyl substituted with heteromonocyclic group,

$R^4$ is lower alkyl,

or a salt thereof,

to give a compound of a formula (Id):



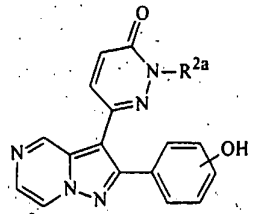
(Id)





wherein $R^2$ is as defined above, or a salt thereof, or

(4) reacting a compound of the formula (Ie):



(Ie)

wherein $R^{2a}$ is as defined above or a salt thereof,

with a compound of the formula (IV):

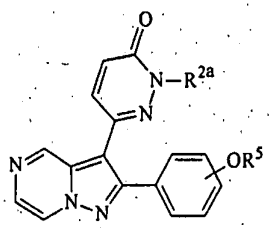
$R^5$-X (IV)

wherein $R^5$ is lower alkyl, and

X is a leaving group,

or a salt thereof,

to give a compound of the formula (If):



(If)

wherein $R^{2a}$ and $R^5$ are as defined above or a salt thereof.

7. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

8. A method for preventing or treating a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation,

asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack and angina pectoris, which comprises administering the compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

9. The compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

10. The compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an adenosine antagonist.

11. The compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an $A_1$ receptor and $A_2$ receptor dual antagonist.

12. A process for preparing a pharmaceutical composition which comprises admixing the compound of claim 1 or a pharmaceutically acceptable sat thereof with a pharmaceutically acceptable carrier.

13. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof for the production of a pharmaceutical composition for the therapy of diseases on which an adenosine antagonist is therapeutically effective.





14. A method for evaluation of adenosine antagonim which comprises use of compound of claim 1 or a pharmaceutically acceptable sat thereof.

# INTERNATIONAL SEARCH REPORT

I. ...national Application No
PCT/JP 00/08008

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/495 A61P25/28 A61P25/16 A61K25/22
A61P9/04 A61P1/04 A61P1/18 A61P13/12 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | EP 0 379 979 A (FUJISAWA)<br>1 August 1990 (1990-08-01)<br>page 2, line 3 - line 24; claims; examples<br>4,28,29 | 1-14 |
| Y | US 5 773 530 A (AKAHANE ET. AL.)<br>30 June 1998 (1998-06-30)<br>column 1, line 19 -column 2, line 24;<br>claims; example 1 | 1-14 |
| Y | EP 0 467 248 A (FUJISAWA)<br>22 January 1992 (1992-01-22)<br>cited in the application<br>page 2, line 3 - line 29; claims; examples<br>1,2,5--12,21-41,49-69 | 1-14 |

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

*A* document defining the general state of the art which is not considered to be of particular relevance

*E* earlier document but published on or after the international filing date

*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

*O* document referring to an oral disclosure, use, exhibition or other means

*P* document published prior to the international filing date but later than the priority date claimed

*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

*&* document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 2 February 2001 | 20 02 01 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Helps, I |

Form PCT/ISA/210 (second sheet) (July 1992)

1

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 00/08008

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 14 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

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Information on patent family members

International Application No
PCT/JP 00/08008

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